monoclonal autoantibody selected from the group consisting of SCH 94.03 and antigen binding fragments thereof.

21. (Amended) A method of treating a demyelinating disease of the central nervous system in a mammal in need of such therapy which comprises administering to said mammal an effective amount of a monoclonal autoantibody selected from the group consisting of SCH 94.03 and antigen binding fragments thereof.

REMARKS

The foregoing amendments and the following remarks are submitted in response to the communication dated May 7, 2001.

Status of the Claims

Claims 1-4, 9-14, and 19-21 are pending in the application. Claims 1, 9, 19, 20 and 21 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' Specification.

The Specification Fully Enables the Claimed Invention

The Examiner has rejected claims 1-4, 9-14 and 19 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that the Specification does not enable any person skilled in the art to which it pertains, or with which it is most connected, to make and use the

invention commensurate in scope with these claims. The Examiner remarks that the Specification, while being enabling for methods of stimulating remyelination or treating demyelinating disease in a mammal by administering an effective amount of certain monoclonal antibodies (specifically noted on page 3 of the Office Action are A2B5 and SCH 79.08), it does not reasonably provide enablement for antibodies 01, 04, HNK-1, isolated or synthetic autoantibodies for stimulation of remyelination.

With respect to antibodies 01, 04 and HNK-1, the only remaining issue is the public availability of the specific antibody clones. The Examiner remarks that Applicants are claiming the HNK-1 clone and that "neither Exhibit A nor Exhibit B provides for the sale of the HNK-1 clone". In addition, the Examiner states " As to Exhibit C, the designation as a distributor is not an indication that the HNK-1 clone is publicly available with unrestricted access by these companies (i.e. for sale)". Applicants respectfully disagree and submit that the HNK-1 antibody is publicly available. Applicants point out that the Examiner may have confused the order or lettering of the Exhibits submitted in our May 9, 2000 response. Exhibit D (inadvertently referred to as Exhibit C by the Examiner) provides a list of distributor information from the ATCC website for the HNK-1 antibody clone. Included on the list of distributors are ATCC, and Becton Dickinson Immunocytochemistry Systems. As provided and demonstrated in Exhibit C by Applicants, Becton Dickinson (BD) Immunocytochemistry Systems is selling CD 57, clone HNK-1. In addition, Applicants provide evidence in the attached Exhibit I that, as indicated in the prior Exhibit D, ATCC offers TIB-200, or the HNK-1 clone, deposited by T. Abo and C. Balch, for sale. In addition, Applicants have further identified, by straightforward world wide web searching readily performed by the

skilled artisan, that Lab Vision Corporation additionally offers the HNK-1 clone for sale (Exhibit J). Thus, Applicants submit that the HNK-1 antibody is publicly available and is, in fact, offered for sale by several sources.

Applicants similarly assert that the O1 and O4 antibodies are publicly available and for sale. Applicants again point to the evidence presented in the earlier provided Exhibit E showing that scientific studies have been performed over more than eighteen years by various laboratories worldwide using the O1 and O4 antibodies. Roche Molecular Biochemicals USA, as evidenced by Exhibit F, offers the O1 and O4 antibodies for sale. Similarly, as evidenced by Exhibit G and the attached Exhibit K, Chemicon International offers the same O1 and O4 antibodies, even particularly referencing Roche Catalog Number 1451014 and 1518925 respectively for each of these antibodies. Chemicon International clearly and particularly references the original O1 and O4 antibody isolation by the laboratory of Dr. Melitta Schachner in its references 1) to Sommer, I. and Schachner M. *Dev Biol* (1981) 83:311-327 , which is entitled "Monoclonal antibodies (O1 to O4) to oligodendrocyte cell surfaces: an immunocytological study in the central nervous system" and 2) to Schachner, M. et al *Dev Biol* (1981) 83:323-338, which is entitled "Developmental expression in central and peripheral nervous system of oligodendrocyte cell surface antigens (O antigens) recognized by monoclonal antibodies", which report the isolation of the O1 and O4 antibody clones, referred to by Applicants and as referenced in the Specification including at page 10, lines 4-30. Applicants herewith as Exhibit L provide a copy of a declaration by inventor Moses Rodriguez, submitted in co-pending related application U.S.S.N. 08/779,784, stating and establishing that the O1 and O4 antibodies offered for sale by Roche Molecular Biochemicals

USA are the same as the O1 and O4 antibodies provided and claimed in the instant Application. Thus, Applicants submit that the O1 and O4 antibodies are publicly available and are, in fact, offered for sale by commercial sources.

With regard to isolated or synthetic autoantibodies, the Examiner asserts that Applicants' Exhibit H is not persuasive because it describes the use of "isolated and purified polyclonal human IgG or IgM" and "it does not describe isolated or synthetic autoantibodies". Applicants respectfully disagree. Exhibit H submitted by Applicants in their May 9, 2000 response is a paper by Warrington, A.E. et al (including inventors L.R. Pease and M. Rodriguez) entitled "Human Antibodies Promote Remyelination of Spinal Cord Lesions in a Model of Multiple Sclerosis," now published as Warrington, et al (2000) PNAS 97(12):6820-6825. Exhibit H, in its Introduction at page 4 states the following:

> Since polyreactive mouse IgM mAbs promote remyelination, we hypothesized that polyclonal human IgM, potentially enriched Abs, would be a more effective treatment of demyelinating disease than polyclonal human IgG, an established therapy for immune-mediated disorders. Treatment of chronically TMEV-infected mice with polyclonal human IgM resulted in enhanced remyelination compared to polyclonal human IgG. Two human mAbs were also identified, using an antigen-independent strategy, which promoted remyelination to a degree equivalent to polyclonal human IgM. We suggest that human remyelination-promoting mAbs may be an easily implemented, effective therapy for human demyelinating disease.

Thus, Exhibit H describes the isolation and characterization of human autoantibodies - both polyclonal human IgM antibodies and isolated human monoclonal autoantibodies. Specifically, in addition to demonstrating that isolated polyclonal human IgM stimulates remyelination in the spinal cords of TMEV-infected mice [Table 1 of Exhibit H], the Exhibit H manuscript describes the following: (a) the isolation of human monoclonal antibodies,

specifically serum-derived human monoclonal IgMs (sHIgMs), sera-derived human monoclonal IgGs (sHIgGs), and Epstein Barr virus-immortalized human peripheral B-cell clone derived IgMs (ebvHIgMs); (b) the ability of isolated human monoclonal antibodies to bind to an antigen which is a normal constituent of the body - thus, their characterization as autoantibodies - including the ability of isolated human monoclonal antibodies to bind to glial cells (oligodendrocytes) [Figures 2, 3, 4 and 5 of Exhibit H]; (c) the ability of isolated human monoclonal autoantibodies to stimulate remyelination in the spinal cords of TMEV-infected mice [Table 1 of Exhibit H]; and (d) the light and heavy chain variable domain sequences of remyelination promoting human monoclonal antibodies [Figure 6 of Exhibit H]. Numerous human monoclonal autoantibodies were isolated and, importantly, these antibodies were isolated using standard methods known to the skilled artisan from different human individuals - both normal individuals and individuals with distinct pathological conditions. These results demonstrate that in addition to human polyclonal autoantibodies and similar to mouse monoclonal antibodies SCH94.03, SCH79.08, A2B5, O1, O4, HNK-1, human monoclonal autoantibodies capable of inducing remyelination can be isolated or made using conventional methodology known to the skilled artisan, even as of the earliest priority date of the instant Application (April 29, 1994). Sequences determined from these monoclonal autoantibodies (as shown in Figure 6 for remyelination promoting human monoclonal antibodies sHIgM22 and ebvHIgM MSI19D10), can be utilized by the skilled artisan in generating and testing synthetic autoantibodies, genetically altered or generated by recombinant techniques, using methods and tests described in the Specification and known to the skilled artisan. In conclusion, Applicants submit that isolated or synthetic monoclonal autoantibodies which are capable of stimulating

remyelination are enabled by the Specification and can readily be made or derived by the skilled artisan, using the teachings of the Specification and conventional methods known to the skilled artisan.

Applicants have above amended claims 1, 9 and 19 to more particularly point out and distinctly claim the invention. In particular, Applicants have clarified the term "isolated autoantibody" to refer to "monoclonal autoantibody". As detailed above, the making or isolation and testing of monoclonal autoantibodies capable of inducing remyelination in central nervous system axons, is clearly enabled by the Specification and conventional methods known to the skilled artisan. Applicants further point out that "synthetic autoantibody capable of inducing remyelination of central nervous system axons" refers to an autoantibody made by a synthetic process, including wherein elements are combined to form a coherent whole, particularly as described in the Specification, including at page 42, lines 18-19, a monoclonal antibody that is genetically altered. Synthetic autoantibody thus includes but is not limited to: autoantibody prepared synthetically by recombinant means known to the skilled artisan, recombinant generation of antibodies being a known generic technique (page 8, lines 18-19); humanized autoantibody, for instance, by the substitution of human antibody nucleotide sequences in non-variable regions of the murine mAb to reduce immunogenicity (page 42, lines 19-20); an antibody molecule having a plurality of antibody combining sites, each immunospecific for a different antigen (page 9, lines 20-23); bi-specific (chimeric) autoantibodies (page 8, lines 15-19); and autoantibodies including other functionalities, including suiting them for additional diagnostic use conjuctive with their capability of modulating - activity stimulating the remyelination of CNS axons (page 8, lines20-23). The

skilled artisan can readily generate synthetic autoantibodies, or genetically altered autoantibodies, using his high level of skill and knowledge and the methods and tests described in the Specification, including but not limited to the disclosed sequences of the remyelinating autoantibodies.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected claims 1-4, 9-14 and 19 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

The Examiner rejects Claims 1, 9 and every claim dependent thereon as indefinite because they recite an improper Markush language in the use of the word "or" in the claims. Applicants have above amended claims 1 and 9 to correct the Markush language.

Claims 4 and 13 are objected to as indefinite in that the term "monoclonal antibody" lacks antecedent basis in the claim from which each depends. Applicants have above amended claims 1, 9, 20 and 21 to correct the antecedent basis.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 35 U.S.C. 112, second paragraph, rejection is obviated and should be withdrawn.

The 35 U.S.C. 102 Rejections

The Examiner has rejected Claim 19 under 35 U.S.C. 102(b) as anticipated by Abo et

al (J. Immunol., 127:1024-1029, 1981) or American Type Culture Collection Catalog, 1992, page 435, which the Examiner asserts teach the monoclonal antibody HNK-1 and anticipate the product claim of HNK-1. Applicants have above amended Claim 19 and assert that the rejection is now moot.

The Examiner further rejects Claim 19 under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter, based on the American Type Culture Collection Catalog, 1992, page 435. Applicants have above amended Claim 19 and assert that the rejection is now moot and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Rodriguez, et al.

SERIAL NO. : 08/692,084 EXAMINER : P. Duffy

FILED : August 8, 1996 ART UNIT : 1645

FOR : PROMOTION OF CENTRAL NERVOUS SYSTEM REMYELINATION USING MONOCLONAL AUTOANTIBODIES

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of stimulating remyelination of central nervous system axons in a mammal which comprises administering to said mammal an effective amount of a[n] monoclonal autoantibody selected from the group consisting of SCH 79.08, 01, 04, A2B5, HNK-1, antigen binding fragments thereof, [and isolated] monoclonal autoantibody capable of inducing remyelination of central nervous system axons and [or] synthetic autoantibody capable of inducing remyelination of central nervous system axons.

9. (Amended) A method of treating a demyelinating disease of the central nervous system in a mammal in need of such therapy which comprises administering to said mammal an effective amount of a[n] monoclonal autoantibody selected from the group consisting of SCH 79.08, 01, 04, A2B5 and HNK-1, antigen binding fragments thereof, [and isolated] monoclonal autoantibody capable of inducing remyelination of central nervous system axons and [or] synthetic autoantibody capable of inducing remyelination of

central nervous system axons.

19. (Amended) A pharmaceutical composition comprising as the active agent, a[n] monoclonal autoantibody selected from the group consisting of an antigen binding fragment of SCH 79.08, [and HNK-1; and isolated] monoclonal autoantibody capable of inducing remyelination of central nervous system axons and [or] synthetic autoantibody capable of inducing remyelination of central nervous system axons.

20. (Amended) A method of stimulating remyelination of central nervous system axons in a mammal which comprises administering to said mammal an effective amount of a[n] monoclonal autoantibody selected from the group consisting of SCH 94.03 and antigen binding fragments thereof.

21. (Amended) A method of treating a demyelinating disease of the central nervous system in a mammal in need of such therapy which comprises administering to said mammal an effective amount of a[n] monoclonal autoantibody selected from the group consisting of SCH 94.03 and antigen binding fragments thereof.